Utilizing endogenous transport systems to ferry therapeutic agents across the BBB is an active area of.3 research.These findings indicate that under conditions of neuroinflammation and BBB dysfunction, the absence of these genes exacerbates both peripheral and CNS inflammation, highlighting the significance of the immune system and the crosstalk between the periphery and the CNS in PD. In a three-dimensional model replicating the BBB, it was noted that astrocytes carrying the LRRK2 G2019S mutation displayed a pro-inflammatory profile and induced changes in the morphology and function of brain blood vessels [46].Several clinical studies, including functional imaging of human patients, analysis of postmortem brain specimens, permeability assessments of drugs used for PD treatment, analysis of albumin/IgG levels in the CSF, and animal models induced with toxins, have identified diverse pathological mechanisms responsible for disrupting the BBB [47].Blood-Brain Barrier and Blood-Cerebrospinal Barrier in PD The blood-brain barrier (BBB), composed of brain endothelial cells, and the blood- CSF barrier (BCSF), formed by the tight junctions between choroid plexus epithelial cells, are two crucial anatomical barriers that constitute the primary interface between the extracellular fluids of the brain and the bloodstream [45].Specifically, in PARKIN and PINK1 knockout mice subjected to active EAE, an animal model of neuroinflammation characterized by disrupted BBB, there was a reduced number of astrocyte cells observed during the later chronic stages of the disease, especially in aged mice [24,26].This oxidative stress harms intercellular junctions, contributes to abnormal cerebral angiogenesis, results in neurovascular decoupling, and actively participates in and exacerbates vascular inflammation [48].While it remains uncertain whether BBB dysfunction is an early event or a consequence of the primary insult in these diseases, it appears that astrocytes play a pivotal role in connecting the pathological processes occurring in the CNS and the periphery through a compromised BBB.These barriers serve as the foremost guardians, not only regulating the passage of various circulating substances between brain fluids and blood but also governing interactions between the peripheral immune system and the CNS [45].Further examination of postmortem human brain tissue confirmed that the vascular characteristics observed in the in vitro model closely corresponded to alterations seen in the brains of individuals with sporadic PD [46].Several therapeutic approaches are being explored to target the BBB and BCSF barrier in PD. Lipid and polymeric-based nanoparticles can be engineered to encapsulate therapeutic agents and navigate the BBB.Among the factors contributing to BBB disruption, notable attention has been directed toward phenotypic changes in astrocytes and endothelial cells, which, together with pericytes, constitute the neurovascular unit [47].Similarly, DJ-1 deficiency can disrupt astrocyte-mediated repair processes through the destabilization of Sox9 and impair the astrogliosis response [52].Dysfunctional astrocytes were observed in PD genetic animal .models